

WHAT IS CLAIMED IS:

1. A recombinant herpes simplex virus incapable of expressing an active $\gamma_134.5$ gene product and comprising an expressible cytokine-encoding DNA.
- 5 2. The recombinant herpes simplex virus of claim 1 wherein said virus lacks all or part of said $\gamma_134.5$ genes.
3. The recombinant herpesvirus of claim 1 wherein said cytokine-encoding DNA is selected from the group consisting of IL-1-, IL-2-, IL-4-, IL-5-, IL-6-, IL-7-, IL-10-, gamma interferon-, and tumor necrosis factor α encoding DNAs.
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4. The recombinant herpes simplex virus of claim 3 wherein said virus comprises $\gamma_134.5$ genes having a deletion of a portion of a coding sequence of said $\gamma_134.5$ genes, said deletion comprising a Bst EII-StuI fragment of said $\gamma_134.5$ genes.
- 15 5. The recombinant herpes simplex virus of claim 1 wherein said virus comprises $\gamma_134.5$ genes having a stop codon at a Bst EII site in said $\gamma_134.5$ genes.
6. The recombinant herpesvirus of claim 5 wherein said cytokine-encoding DNA is selected from the group of DNAs consisting of IL-1-, IL-2-, IL-4-, IL-5-, IL-6-, IL-7-, IL-10-, gamma interferon-, and tumor necrosis factor α encoding DNAs.
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7. The recombinant herpes simplex virus of claim 1 wherein said expressible cytokine-encoding DNA is under the promoter-regulatory control of a herpes simplex virus gene promoter.

5 8. The recombinant herpes simplex virus of claim 7 wherein said herpes simplex virus gene promoter is an EGR-1 promoter.

9. The recombinant herpes simplex virus of claim 1 wherein said cytokine-encoding DNA is under the promoter-regulatory control of a synthetic herpes simplex virus-derived promoter.

10 10. The recombinant herpes simplex virus of claim 9 wherein said synthetic herpes simplex virus-derived promoter comprises a herpes simplex virus α gene promoter fragment operatively linked 5' to a herpes simplex virus γ gene promoter fragment.

15 11. The recombinant herpes simplex virus of claim 10 wherein said α gene promoter fragment comprises promoter sequences upstream of the transcription initiation site of the $\alpha 4$ gene and said γ gene promoter fragment comprises a transcription initiation site and the 5' transcribed non-coding sequence of the $\gamma_1 U_L 19$ gene.

12. The recombinant herpes simplex virus of claim 1 wherein said $\gamma_1 34.5$ genes are replaced by said expressible cytokine-encoding DNA.

20 13. The recombinant herpes simplex virus of claim 1 wherein said virus comprises two or more copies of said DNA encoding cytokine.

14. A recombinant herpes simplex virus type 1, said virus comprising a DNA encoding IL-4 and lacking $\gamma_1 34.5$ genes.

15. The recombinant herpes simplex virus type 1 of claim 14 wherein said IL-4 encoding DNA has replaced said $\gamma_134.5$ genes.

16. The recombinant virus of claim 14 wherein said DNA encoding IL-4 DNA is under the promoter regulatory control of an EGR-1 promoter.

5 17. The recombinant virus of claim 13 wherein said IL-4 encoding cDNA further comprises a polyadenylation signal.

18. The recombinant virus of claim 14 wherein said polyadenylation signal is a hepatitis B virus-derived polyadenylation signal.

10 19. A method for treating neoplastic disease of the central nervous system, the method comprising administering to a target tumor, a recombinant herpes simplex virus incapable of expressing an active $\gamma_134.5$ gene product and comprising an expressible cytokine-encoding DNA.

20. The method of claim 16 wherein said recombinant herpes simplex virus lacks all or part of said $\gamma_134.5$ genes.

15 21. The method of claim 20 wherein said cytokine-encoding DNA is selected from the group of DNAs consisting of IL-1-, IL-2-, IL-4-, IL-5-, IL-6-, IL-7-, IL-10-, gamma interferon-, and tumor necrosis factor- α encoding DNAs.

20 22. The method of claim 16 wherein said recombinant herpes simplex virus comprises $\gamma_134.5$ genes having a stop codon at a Bst EII site in said $\gamma_134.5$ genes.

23. The method of claim 22 wherein said cytokine encoding DNA is selected from the group of DNAs consisting of IL-1-, IL-2-, IL-4-, IL-5-, IL-6-, IL-7-, IL-10-, gamma interferon-, and tumor necrosis factor- α encoding DNAs.

5 24. The method of claim 19 wherein said recombinant herpes simplex virus comprises $\gamma_134.5$ genes lacking a portion of the coding sequence corresponding to a Bst EII/StuI restriction fragment of said $\gamma_134.5$ genes.

25. The method of claim 19 wherein said expressible cytokine-encoding DNA is under the promoter-regulatory control of a herpes simplex virus gene promoter.
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26. The method of claim 23 wherein said herpes simplex virus promoter is an EGR-1 promoter.

27. The method of claim 19 wherein said cytokine-encoding DNA is under the promoter regulatory control of a synthetic herpes simplex virus derived promoter.
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28. The method of claim 27 wherein said synthetic herpes simplex derived promoter comprises a herpes simplex virus α gene fragment operatively linked 5' to a herpes simplex virus γ gene promoter fragment.

6 29. The method of claim 28 wherein said α gene promoter fragment comprises promoter sequences upstream of the transcription initiation site of said α gene promoter fragment comprises the transcription initiation site and the 5' transcribed non-coding sequence of the γ_1U_L19 gene.
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30. The method of claim 20 wherein said $\gamma_134.5$ genes are replaced by said expressible cytokine-encoding DNA.

5 31. A pharmaceutical composition comprising in a pharmaceutically acceptable carrier, diluent, or adjuvant, a recombinant herpes simplex virus incapable of expressing an active $\gamma_134.5$ gene product, said virus comprising an expressible cytokine-encoding DNA.

10 32. A pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, diluent, or adjuvant, a herpes simplex virus type 1 genome comprising two copies of a cDNA encoding IL-4, each under the promoter regulatory control of a herpes simplex virus EGR-1 promoter and each having at its 3' terminus a hepatitis B virus polyadenylation signal, and wherein said IL-4 encoding cDNAs have replaced viral $\gamma_134.5$ genes in said viral genome.